Relation of omega-3 fatty acid and dietary fish intake with brachial artery flow-mediated vasodilation in the Multi-Ethnic Study of Atherosclerosis[1–3]

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ABSTRACT

Background: The relation between dietary fish intake and brachial artery measures, including brachial artery flow-mediated dilation (FMD), has not been well established across sex and racial-ethnic groups.

Objective: We hypothesized that consumption of nonfried fish and plasma phospholipid measures of long-chain omega-3 (n–3) fatty acids would be positively associated with larger FMD in men and women across racial-ethnic groups.

Design: We investigated cross-sectional associations of brachial artery measures with fish intake (ascertained with a food-frequency questionnaire) and plasma phospholipid omega-3 concentrations in 3045 adults, aged 45–84 y, who were free of clinical cardiovascular disease.

Results: In overall multivariate-adjusted analyses, there were no significant associations between fish intake or any brachial artery measures. However, when stratified by sex, there was an association between the highest quartile of nonfried fish consumption and a 0.10-mm lower (1 SD) brachial artery diameter in men ($P = 0.01$) and a 0.27% smaller FMD in women ($P = 0.02$) compared with the lowest quartile of nonfried fish intake in each respective sex strata. When stratified by race-ethnicity and race-ethnicity by sex, additional heterogeneity was noted, but results were difficult to interpret because of small sample sizes. Plasma phospholipid omega-3 concentrations showed a similar directionality of association with brachial artery measures observed for nonfried fish consumption, although statistical significance was not achieved in fully adjusted models.

Conclusion: This study indicates that the association between nonfried fish intake and baseline brachial artery size varies by sex, with suggestive evidence of sex differences in the association between nonfried fish intake and FMD. *Am J Clin Nutr* 2010;92:1204–13.

INTRODUCTION

Multiple epidemiologic, observational, and interventional studies have shown an inverse relation between fish consumption and cardiovascular events and death (1–6). Several mechanisms have been reported that may be responsible for these beneficial associations (7–10). One purported mechanism includes the effect of omega-3 (n−3) fatty acids on lipid bilayer composition and subsequent improvement in membrane fluidity, which may play an important role in endothelial function (11–13).

Flow-mediated dilation (FMD) is a noninvasive surrogate for endothelial function, which is, in part, dependent on endothelial production and the release of nitric oxide (14–16). Large, prospective cohort studies suggested that FMD may be a useful tool to evaluate early atherosclerotic disease, particularly in healthy individuals with low Framingham risk scores, and a larger FMD has been shown to be predictive of decreased incident cardiovascular events (fully adjusted hazard ratios ranged from 0.84 to 0.91) (17–20). FMD has also been shown to be influenced by the intake of fish oils in randomized trials with durations as short as 2 wk (21, 22). However, there are few studies that examined the effects of dietary fish consumption on FMD, and the relation between fish intake and FMD in different racial-ethnic groups are lacking.

The main objective of the current study was to examine the relations of endothelial dysfunction, as measured by FMD, with fish intake and concentrations of plasma phospholipid omega-3 fatty acid [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] by using data from the Multi-Ethnic Study of Atherosclerosis (MESA). We hypothesized that consumption of nonfried fish foods as well as plasma phospholipid EPA and DHA concentrations would be positively associated with larger FMD in men and women across racial-ethnic groups. In addition, we examined the relation of other brachial artery measures (baseline brachial diameter and maximal diameter) with fish intake and plasma phospholipid omega-3 fatty acid concentrations for exploratory purposes because others observed an association of increased cardiovascular events with larger baseline brachial artery diameters (17, 18).

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METHODS

Study population and data collection

MESA is a prospective cohort study that began in July 2000 to investigate the prevalence, correlates and progression of subclinical cardiovascular disease (CVD) in individuals without known CVD at baseline. The main cohort included 6814 women and men aged 45–84 y old at baseline who were recruited from 6 US communities (Baltimore, MD; Chicago, IL.; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St Paul, MN). MESA cohort participants were 38% white (n = 2624), 28% black (n = 1895), 22% Hispanic (n = 1492), and 12% Chinese (n = 803). Details of the MESA study design were documented previously (23). A variety of noninvasive measures of subclinical disease, including brachial FMD, were obtained during the first examination of the MESA cohort (July 2000 to August 2002). In the current study, we excluded subjects who had missing data on both fish intake (n = 364) and brachial FMD (n = 3589) and subjects with missing covariates that were used in the study (n = 92). The total sample size after these exclusions was 3045. This study was approved by the Institutional Review Boards of each study site, and written informed consent to participate in the study was obtained from all participants.

Dietary assessment

A detailed description of the MESA food-frequency questionnaire (FFQ) was described previously (24). At baseline, participants recorded the serving size (small, medium, or large) and frequency (times per day, week, or month) that they consumed each FFQ item. Responses were converted to servings per day by multiplying consumption frequency by reported serving size, with weights of 0.5, 1.0, and 1.5 applied to small, medium, and large serving sizes, respectively (24).

The MESA FFQ was modified from the FFQ used in the Insulin Resistance Atherosclerosis Study to include unique Chinese foods and to collect supplemental information (23, 25). The validity of the FFQ was assessed by comparison with eight 24-h dietary recalls in non-Hispanic white, black, and Hispanic persons in the Insulin Resistance Atherosclerosis Study (25). Ten FFQ items included information about fish and shellfish consumption, which were then categorized by types as follows: nonfried fish (2 items; *1*) tuna, salmon, sardines, sashimi, or sushi and *2*) other broiled, steamed, baked, or raw fish, such as trout, sole, halibut, poke, and grouper); shellfish (1 item; nonfried shrimp, lobster, crab, oysters, and mussels); fish-containing mixed dishes (6 items; fish in enchiladas, burritos, quesadilla, pasta, stew, gumbo, paella, and salad); and fried fish (1 item; any fried fish or fish sandwich, fried shrimp, and calamari). A recent validation study in dietary macronutrient intake and plasma lipids showed the criterion performance of the MESA FFQ (26), and associations between fish intake and plasma fatty acids were previously reported (27). In addition, we confirmed a positive, statistically significant association between nonfried fish intake and plasma phospholipid EPA and DHA concentrations within our sample population (overall $r = 0.29$, $P < 0.0001$; data not shown). The strength of this relation was similar to that observed by others (28), and other types of fish did not show significant relations with fatty acids after adjustment for nonfried fish.

For statistical analyses, the frequency of fish consumption was further classified into 4 main categories for each fish type *1*): rare or never, *2*) 1–3 times/mo, *3*) 1–2 times/wk, and *4*) >2 times/wk. Quartiles ranks were created on the basis of the sample range. This strategy was adopted on the basis of previous data that showed a threshold effect of nonfried fish intake, with consumption of nonfried fish once weekly resulting in remarkably lower incidence of sudden cardiac death compared with little or no nonfried fish intake, as well as on the basis of data that suggested a plateau effect with a nonfried fish intake of twice weekly (27, 28). Additional analyses including comparisons of <1 serving compared with ≥ 1 serving of nonfried fish/wk on brachial measures were also examined within this cohort, and similar patterns were observed (data not shown).

Plasma phospholipid extraction

Fasting blood samples were collected, and plasma phospholipid fatty acid analyses were performed at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, MN) as previously described (n = 1642) (23, 29). In brief, plasma lipids were extracted with chloroform and methanol, and thin layer chromatography was used to separate the lipid fractions and isolate phospholipids. Fatty acids were assessed by using gas chromatography with a flame ionization detector, and the concentration of each fatty acid was expressed as a percentage of the total fatty acids. Because EPA and DHA are found together in fatty fish, and therefore, plasma phospholipid values are highly correlated (30), plasma phospholipid concentrations of EPA and DHA were summed for each subject. For statistical analyses, quartile ranks were created on the basis of the sample range of these sums.

Brachial FMD measurement

Brachial FMD was measured in the MESA cohort during the first examination. Participants were excluded if they had uncontrolled hypertension (158 MESA participants were excluded), blood pressures in the left and right arms that differed by >15 mm Hg, a history of Raynaud's phenomenon (55 MESA participants were excluded), a congenital abnormality of the arm or hand (12 MESA participants were excluded), or a radical mastectomy on either side (100 MESA participants were excluded). Participants were examined in the supine position after 15 min rest and after a fast of ≥6 h. A standard blood pressure cuff was positioned around the right arm, 2 inches below the antecubital fossa, and the artery was imaged 5–9 cm above the antecubital fossa. A linear-array multifrequency transducer that operated at 9 MHz (GE Logiq 700 Device; Fairfield, CT) was used to acquire images of the right brachial artery. After obtaining baseline images, the cuff was inflated to 50 mm Hg above the participant's systolic blood pressure for 5 min. Digitized images of the right brachial artery were captured continuously for 30 s before cuff inflation and for 2 min beginning immediately before cuff deflation to document the vasodilator response. A detailed description of the scanning and reading protocol can be found at the MESA website (http://www.mesa-nhlbi.org).

An analysis of the brachial artery videotapes was performed in a nested case-cohort of MESA participants that involved a random sample of MESA participants (subcohort; n = 2,844) and all participants who had an adjudicated cardiovascular event by 10 October 2005 (cases; n = 182). The videotapes were analyzed at the Wake Forest University Cardiology Image Processing Laboratory by using a previously validated semiautomated system (11). The semiautomated readings (media-adventitial interfaces to media-adventitial interfaces) of these digitized images generated the baseline and maximum diameters of the brachial artery from which the percentage FMD was computed as follows:

$$\text{Percentage FMD} = [(\text{maximum diameter} - \text{baseline diameter})/\text{baseline diameter}] \times 100\% \qquad (1)$$

Correlations for repeated measures of baseline diameter, maximum diameter, and percentage FMD were obtained with an original read and a quality-control read scanned on 2 separate days in 40 MESA participants (32 men; 18 white, 2 Chinese, 10 African American, and 10 Hispanic participants) were 0.99, 0.99, and 0.81, respectively.

Statistical analyses

Means and SDs or proportions were calculated for selected variables according to the 4 categories of nonfried fish consumption (**Table 1**). For the primary analysis, the following regression models were used to examine the association between fish consumption (separately by fish type) and brachial artery measures: baseline diameter, maximum diameter after the flow stimulus, and absolute and percentage changes in brachial diameter (percentage FMD). Minimally adjusted (age) and fully adjusted models were used to examine these relations. On the basis of previously published research and univariate tests, we considered a number of potential confounders for inclusion in the fully adjusted models, including BMI, systolic and diastolic blood pressure, diabetes diagnosis (by using the 2003 American Diabetes Association fasting criteria algorithm) (31), hypertension medication, serum triglyceride concentration, ratio of serum total:HDL cholesterol, lipid-lowering medication, exercise, tobacco pack-years, current and former smoking status, alcohol intake, income, education, menopausal status, current hormone replacement therapy, total caloric intake, percentage saturated fat intake, α-linolenic acid intake, linoleic acid intake, vitamin/

TABLE 1
Sample characteristics classified by frequency of nonfried fish intake[1]

	Rare or never (n = 618)	1–3 times/mo (n = 918)	1–2 times/wk (n = 803)	>2 times/wk (n = 706)	P[2]
Age (y)	61 ± 0.39[3]	61 ± 0.32	62 ± 0.34	62 ± 0.38	0.03
Sex (% male)	52.7	48.3	49.1	48.2	0.3
Race (%)					<0.0001
White	27.3	36.1	35.4	38.2	
Black	18.9	23.1	22.2	19.6	
Chinese	11.4	12.7	24.2	30.1	
Hispanic	42.5	28.1	18.1	12.1	
BMI (kg/m^2)	28.7 ± 0.21	28.3 ± 0.17	27.1 ± 0.17	27.0 ± 0.18	<0.0001
At least a high school education (%)	69.8	84	84.1	87.1	<0.0001
Annual income <$50,000 (%)	72.5	61.6	56	50.1	<0.0001
Cigarette smoking					
Pack-years	13.1 ± 1.4	10.1 ± 0.6	8.9 ± 0.6	9.5 ± 0.8	0.004
Current (%)	15.3	12.1	9.9	9.4	0.002
Physical activity, moderate to heavy (MET-h/wk)	6155 ± 239	6020 ± 196	5111 ± 165	5277 ± 192	0.0001
SBP (mm Hg)	126 ± 0.76	125 ± 0.65	123 ± 0.67	125 ± 0.77	0.04
DBP (mm Hg)	72 ± 0.37	71 ± 0.34	72 ± 0.25	72 ± 0.36	0.35
Hypertension medication (%)	29.6	36.4	35.9	36.3	0.02
Lipid concentrations					
Total:HDL	4.3 ± 0.05	4.1 ± 0.04	4.1 ± 0.04	4.0 ± 0.04	<0.0001
Triglyceride concentration (mg/dL)	146 ± 3.4	135 ± 3.4	128 ± 2.5	126 ± 2.9	<0.0001
Cholesterol medication (%)	14.6	14.6	15.6	18.1	0.22
Diabetic (%)	17.1	11.6	12.1	11.9	0.01
Hormone replacement therapy for women (%)	27	35.1	35.6	30.9	0.07
Total energy (kcal/d)	1623 ± 30	1624 ± 26	1599 ± 27	1734 ± 32	0.005
Alcohol (average drinks/wk)	5.8 ± 0.53	4.8 ± 0.32	4.7 ± 0.33	4.5 ± 0.28	0.08
Carbohydrate intake (g/d)	199 ± 3.8	201 ± 3.2	199 ± 3.3	210 ± 3.8	0.1
Saturated fat (% of energy)	11.2	11	10	9.5	<0.0001
Linoleic acid (% of energy)	6.8	6.4	6.7	6.6	0.007
Fruit (servings/d)	1.5	1.7	1.8	2.2	<0.001
Cruciferous vegetables (servings/d)	0.27	0.3	0.42	0.56	<0.0001

[1] MET-h, metabolic equivalent task hours; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[2] Test for trend across quartile ranks of nonfried fish intake.

[3] Mean ± SD (all such values).

mineral supplement use (including vitamins C and E and folate), and polyphenolic-rich food intake (highest quintile compared with others). However, fish intake may influence brachial artery measures via modification of plasma lipid concentrations and blood pressure (ie, inclusion of these variables might represent overadjustment). The inclusion or exclusion of these variables as covariates did not significantly alter the relation between fish intake and brachial FMD. Thus, these covariates were not retained in the final multivariable adjusted model, which included age, sex, race-ethnicity, BMI, current smoking status, educational level, income level, and (in women only) current hormone replacement therapy. Because sex differences in fatty acid metabolism and tissue levels have been described (32, 33), and racial-ethnic differences have been observed in FMD (34), we also chose to stratify analyses by sex and race-ethnicity. When there appeared to be significant differences in fish and brachial artery measures by sex as well as race-ethnicity, formal tests for interaction were performed by using the product of fish × sex and fish × race-ethnicity in separate models. In additional analyses, the association between plasma phospholipid EPA + DHA concentrations and brachial dimensions were examined by using similar age-adjusted and fully adjusted linear models. Stratification by sex and race-ethnicity were also performed for plasma EPA + DHA concentrations for the reasons previously cited; when there appeared to be significant differences in plasma phospholipid EPA + DHA concentrations and brachial artery measures by sex and/or race-ethnicity, formal tests for interactions were performed (ie, the product of EPA + DHA × sex and of EPA + DHA × race-ethnicity were included in separate models). All *P* values were 2-sided, and a *P* value ≤0.05 was considered significant. We used JMP version 8.0 software (SAS Institute Inc, Cary, NC) for analyses.

RESULTS

Participant characteristics

Characteristics of participants according to intakes of nonfried fish are presented in Table 1. Greater nonfried fish consumption was associated with older age, white and Chinese race-ethnicity, lower BMI, higher education, higher income, less tobacco use, lower systolic blood pressure, lower blood lipid concentrations, and a lower prevalence of diabetes. Greater nonfried fish consumption was also associated with lower saturated fat intake and a higher consumption of fruit and vegetables, although greater intake was also associated with lower physical activity levels.

The numbers of subjects in each of the nonfried fish categories were roughly similar overall and after stratification for sex. The

TABLE 2

Brachial artery measures and nonfried fish intake by sex[1]

Brachial measure and fish frequency	Overall (*n* = 3045)				Stratified by sex							
					Men (*n* = 1500)				Women (*n* = 1377)[2]			
	Age-adjusted		Fully adjusted[3]		Age-adjusted		Fully adjusted[4]		Age-adjusted		Fully adjusted[4]	
	Values	*P*	Values	*P*	Values	*P*	Values	*P*	Values	*P*	Values	*P*
Baseline diameter (mm)[5]												
Never or rare	4.43 ± 0.03	<0.0001	4.47 ± 0.04	0.45	4.91 ± 0.04	<0.0001	4.95 ± 0.06	0.01	3.90 ± 0.03	0.39	4.01 ± 0.05	0.17
1–3 times/mo	4.32 ± 0.03	—	4.44 ± 0.04	—	4.91 ± 0.03	—	4.97 ± 0.06	—	3.76 ± 0.03	—	3.94 ± 0.05	—
1–2 times/wk	4.27 ± 0.03	—	4.42 ± 0.04	—	4.77 ± 0.03	—	4.87 ± 0.06	—	3.79 ± 0.03	—	3.99 ± 0.05	—
>2 times/wk	4.26 ± 0.03	—	4.45 ± 0.04	—	4.72 ± 0.04	—	4.85 ± 0.06	—	3.83 ± 0.03	—	4.05 ± 0.05	—
Maximum diameter (mm)[6]												
Never or rare	4.50 ± 0.004	0.48	4.45 ± 0.01	0.34	5.02 ± 0.01	0.43	4.99 ± 0.01	0.75	3.99 ± 0.01	0.69	3.99 ± 0.01	0.08
1–3 times/mo	4.50 ± 0.003	—	4.45 ± 0.01	—	5.01 ± 0.01	—	4.98 ± 0.01	—	4.00 ± 0.01	—	4.00 ± 0.01	—
1–2 times/wk	4.49 ± 0.003	—	4.44 ± 0.01	—	5.01 ± 0.01	—	4.98 ± 0.01	—	3.98 ± 0.01	—	3.98 ± 0.01	—
>2 times/wk	4.50 ± 0.004	—	4.44 ± 0.01	—	5.02 ± 0.01	—	4.99 ± 0.01	—	3.99 ± 0.01	—	3.98 ± 0.01	—
FMD change (mm)												
Never or rare	0.18 ± 0.004	0.84	0.17 ± 0.01	0.23	0.19 ± 0.01	0.58	0.19 ± 0.01	0.99	0.17 ± 0.005	0.51	0.16 ± 0.01	0.05
1–3 times/mo	0.18 ± 0.003	—	0.14 ± 0.01	—	0.18 ± 0.01	—	0.18 ± 0.01	—	0.18 ± 0.004	—	0.17 ± 0.01	—
1–2 times/wk	0.18 ± 0.003	—	0.16 ± 0.01	—	0.18 ± 0.01	—	0.18 ± 0.01	—	0.17 ± 0.005	—	0.15 ± 0.01	—
>2 times/wk	0.18 ± 0.004	—	0.17 ± 0.01	—	0.19 ± 0.01	—	0.19 ± 0.01	—	0.17 ± 0.005	—	0.15 ± 0.01	—
FMD change (%)[7]												
Never or rare	4.28 ± 0.11	0.51	4.04 ± 0.16	0.20	3.96 ± 0.13	0.16	4.04 ± 0.20	0.63	4.63 ± 0.16	0.71	4.04 ± 0.25	0.02
1–3 times/mo	4.52 ± 0.09	—	4.15 ± 0.16	—	3.78 ± 0.11	—	3.82 ± 0.20	—	5.12 ± 0.13	—	4.49 ± 0.24	—
1–2 times/wk	4.33 ± 0.09	—	3.90 ± 0.16	—	3.92 ± 0.12	—	3.92 ± 0.20	—	4.72 ± 0.14	—	3.87 ± 0.24	—
>2 times/wk	4.47 ± 0.10	—	3.94 ± 0.17	—	4.16 ± 0.13	—	4.08 ± 0.21	—	4.76 ± 0.15	—	3.77 ± 0.26	—

[1] All values are means ± SDs. FMD, brachial artery flow-mediated dilation.

[2] Adjustment for current hormone replacement therapy resulted in a sample-size loss of 168 women.

[3] Multivariate linear regression analysis with adjustment for age, sex, race-ethnicity, BMI, current smoking status, educational level, and income level.

[4] Multivariate linear regression analysis with adjustment for age, race-ethnicity, BMI, current smoking status, educational level, income level, and (in women) current hormone replacement therapy.

[5] *P* value for (nonfried fish × sex) interaction = 0.0001.

[6] Adjusted for baseline artery diameter.

[7] [(Maximum diameter – baseline diameter)/baseline diameter] × 100%. *P* value for (nonfried fish × sex) interaction = 0.09.

median intake of the sex- and race-ethnicity–combined sample was ≈3 servings/mo, which corresponded to a median plasma phospholipid EPA + DHA percentage of 4.87 ± 2.33%. Of participants, Hispanics consumed nonfried fish the least frequently, with a median intake of 1 time/mo, followed by blacks (median intake: 2–3 times/mo). Whites and Chinese consumed nonfried fish most frequently (median intake: 1 time/wk and 2 times/wk, respectively). When further stratified by sex and race-ethnicity, values were similar. Intakes of other fish groups also showed similar patterns (data not shown).

Fish consumption and brachial artery measures

After adjustment for age, the highest quartiles of nonfried fish intake were significantly associated with a smaller baseline brachial artery diameter compared with that of the lowest quartile of intake ($P < 0.0001$); however, after adjustment for other covariates, this association was no longer significant (**Table 2**). There were no other significant associations between nonfried fish intake and brachial artery measures in either the age-adjusted or fully adjusted overall models.

When analyses were stratified by sex, a significant inverse relation between nonfried fish intake and baseline diameters was observed in men (Table 2). In contrast, in women, greater nonfried fish intake was associated with larger baseline diameters (P = NS) and a smaller percentage FMD ($P = 0.02$; Table 2). Simple inspection of the data comparing men with women suggest that the frequency of nonfried fish intake presented as opposing U-shaped patterns for baseline artery diameter and FMD (**Figure 1**). Tests of interactions between sex and nonfried fish intake for baseline diameter and percentage FMD were performed, and a significant interaction was noted between sex and nonfried fish intake for baseline diameter ($P = 0.0001$ for baseline diameter; $P = 0.09$ for percentage FMD). No other

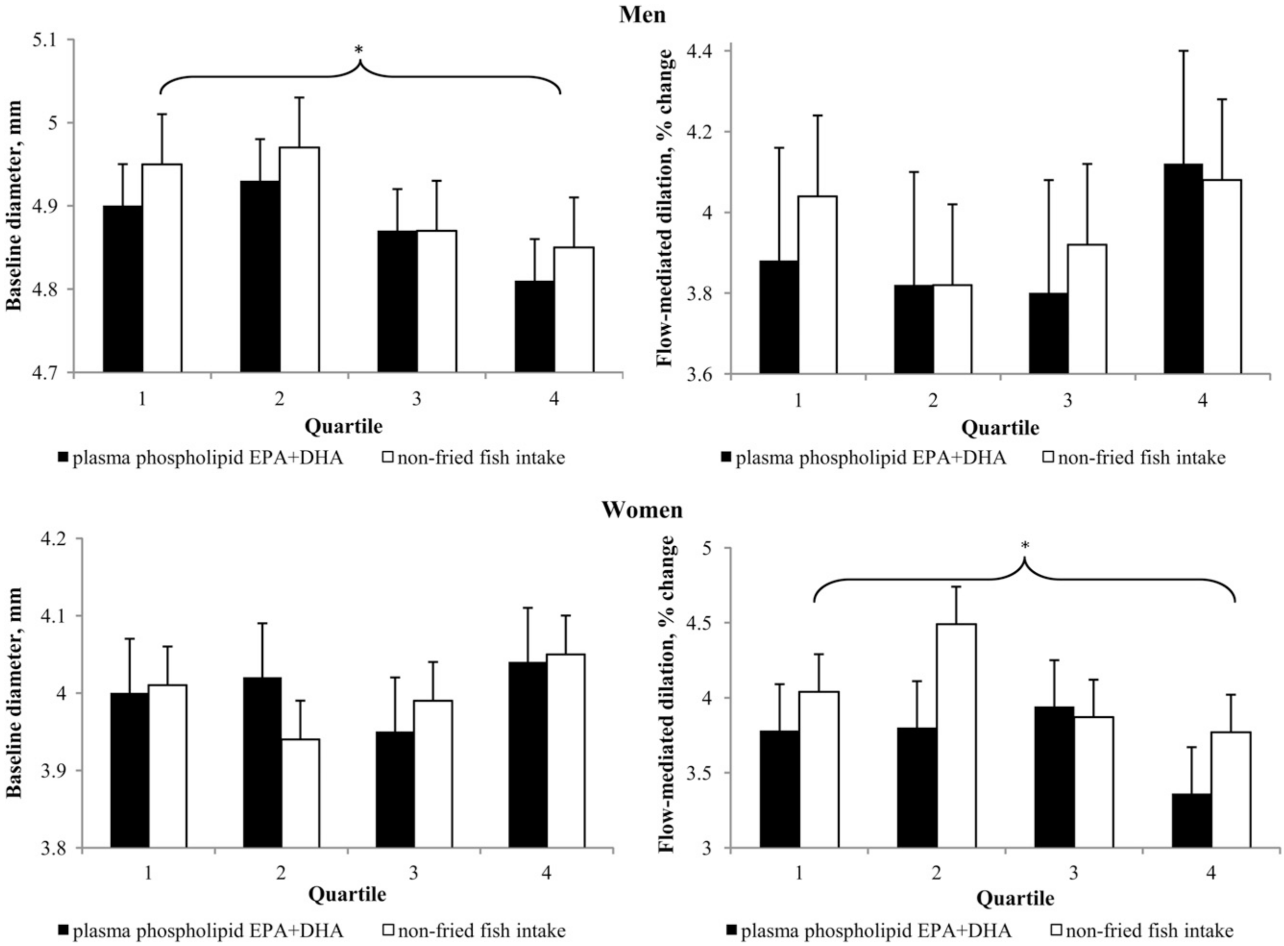

FIGURE 1. Least-squares means (±SDs) of brachial artery measures and concentrations of plasma phospholipid eicosapentaenoic acid and docosahexaenoic acid (EPA+DHA) compared with nonfried fish intake by sex. Results shown were adjusted for age, race-ethnicity, BMI, current smoking status, educational level, income level, and (in women) current hormone replacement therapy. Concentrations of plasma phospholipid EPA+DHA (expressed as percentages of total fatty acids) were summed and ranked into quartiles from lowest to highest on the basis of sample range. The sample size of each plasma phospholipid EPA+DHA quartile for men was as follows: quartile 1 = 204, quartile 2 = 170, quartile 3 = 196, and quartile 4 = 174. The sample size of each plasma phospholipid EPA+DHA quartile for women was as follows: quartile 1 = 159, quartile 2 = 207, quartile 3 = 174, and quartile 4 = 204 (adjustment for current hormone replacement therapy resulted in a sample-size loss of 106 women.) Quartiles of nonfried fish intake were created on the basis of the sample range and represent the frequency of dietary nonfried fish consumption classified as *1*) rare or never, *2*) 1–3 times/mo, *3*) 1–2 times/wk, and *4*) >2 times/wk. The sample size of each nonfried fish intake quartile for men was as follows: quartile 1 = 337, quartile 2 = 425, quartile 3 = 408, and quartile 4 = 343. The sample size of each nonfried fish intake quartile for women was as follows: quartile 1 = 304, quartile 2 = 488, quartile 3 = 425, and quartile 4 = 367. *P for trend < 0.05.

significant associations of any brachial artery measure with consumption of other fish types were observed.

Because other researchers observed significant racial-ethnic differences in FMD (34), data were additionally stratified by race-ethnicity, and a significant inverse association was observed between nonfried fish intake and baseline artery diameters in Hispanics (**Table 3**). Tests of interaction by race-ethnicity were examined and were not significant. Data were further stratified by race-ethnicity and sex, and in these stratified analyses, an inverse association between nonfried fish intake and baseline artery diameters were significant in Hispanic men ($P = 0.01$; data not shown), and an inverse relation between nonfried fish intake and raw FMD (mm change) was significant in Chinese women only ($P = 0.03$; data not shown). However, the numbers of participants within each of these subgroups were small (eg, $n = 367$ for Hispanic men, and $n = 302$ for Chinese women).

Plasma phospholipid EPA + DHA and FMD

Similar to observations of other MESA investigators (who used a different sample size and selection criteria) (27), plasma phospholipid EPA + DHA concentrations were significantly positively correlated with nonfried fish intake across all races and in men and women within our subsample of participants ($r = 0.28$ for men and women, $P < 0.0001$; data not shown). Consistent with dietary nonfried fish consumption, there was an inverse relation noted between baseline artery diameters and plasma phospholipid EPA + DHA concentrations in men, although results were only significant in the age-adjusted model ($P = 0.003$ in the age-adjusted model; data not shown; $P = 0.16$ in the fully adjusted model; Figure 1). In women, a pattern that paralleled the relation with dietary nonfried fish intake and FMD was also observed, but this was not significant (Figure 1). When data were stratified by race-ethnicity, significant inverse associations were observed between plasma phospholipid EPA + DHA concentrations and baseline diameters in Chinese and Hispanics in age-adjusted models but not in fully adjusted models. In addition, a borderline significant association between plasma phospholipid EPA + DHA concentrations and FMD in blacks was observed in fully adjusted models ($P = 0.04$ for the millimeter change in FMD; $P = 0.06$ for percentage change in FMD; **Table 4**) but not in age-adjusted models. Tests for interactions of EPA + DHA × brachial artery measures were nonsignificant ($P = 0.92$). Stratification by sex in addition to race-ethnicity revealed no significant associations between plasma phospholipid EPA + DHA concentrations and brachial measures (data not shown).

DISCUSSION

In the current study, in which we examined the relation between fish consumption and noninvasive measures of endothelial function across racial-ethnic groups, the main finding was that increasing quartiles of nonfried fish intake resulted in disparate responses in baseline artery diameters and FMD in men compared with women. Visual inspection of the data suggested a nearly mirror-image relation among these brachial measures by sex, although statistical significance was only observed for baseline artery diameters in men and FMD in women (Table 2, Figure 1). The second finding of this study was that stratification by race-ethnicity revealed a significant inverse association between nonfried fish intake and baseline artery diameters in Hispanics (Table 3), and although some significant associations were detected between nonfried fish and brachial artery measures after further stratification by sex, sample sizes were quite small and results were difficult to interpret with confidence. Last, similar patterns were also observed between plasma phospholipid EPA + DHA concentrations and brachial artery measures when stratified by sex and race-ethnicity, although results were not significant in each case (Table 4; Figure 1).

The clinical implications of these findings are not yet certain. Other MESA investigators showed associations between nonfried fish consumption and lower concentrations of inflammatory biomarkers and markers of endothelial activation (27, 36). In addition, greater FMD and smaller baseline artery diameters were associated with decreased incident cardiovascular events within the MESA cohort (18), and an inverse relation between FMD and left ventricular mass has also been noted (35). Our subsample had a median plasma phospholipid EPA + DHA concentration that was comparable with that observed by others in subjects with similar intakes of nonfried fish and would be expected to reduce the incidence of sudden cardiac death substantially compared with the risk for individuals in the lowest quartile of nonfried fish intake (37). Thus, the inverse association between nonfried fish intake and FMD observed in women in the current study is unexpected. Additional analyses are warranted to determine whether the relation between nonfried fish intake (and plasma phospholipid concentrations) and other cardiovascular outcomes also vary by sex.

Several lines of evidence suggest there may be important sex differences in metabolic, physiologic, or clinical consequences of dietary fat consumption (38–40). Unfortunately, there are few studies in women that examined the relation between omega-3 fatty acid or fish intake and clinical correlates of CVD and/or incident events, and even fewer studies have included women of different racial-ethnic groups. Although the Nurse's Health Study clearly showed a cardioprotective effect of nonfried fish consumption in a large population of white women (41), results from a recent 12-y prospective cohort of men and women of mixed racial-ethnic groups failed to demonstrate a significant protective effect of nonfried fish consumption in women (42). Of interest, an increased risk in incident cardiovascular events in those who consumed more salted and dried fish was observed within this cohort (42).

Some previous data suggested that omega-3 fatty acid metabolism differs between men and women. Population surveys from New Zealand, the United Kingdom, and Canada showed women had a greater tissue DHA content compared with that of men, regardless of dietary omega-3 intakes, and some population surveys showed variable tissue EPA and docosapentaenoic acid (DPA) contents as well (43–46). Evidence from stable-isotope feeding studies also showed differences in omega-3 metabolism, with women demonstrating a higher capacity to metabolize α-linolenic acid to DHA than did men (32, 47). However, it was also postulated that women may have less ability to retroconvert DHA to EPA and DPA, and experimental studies showed that hormone replacement therapy inhibited such retroconversion (48). Clinical implications of these findings are unclear because both EPA and DHA had beneficial effects on cardiovascular risk factors. It is possible that EPA compared with DHA exhibited varying mechanisms of action on inflammation, lipid oxidation, nitric oxide, or other modulators of endothelial function (49).

TABLE 3

Brachial artery measures and nonfried fish intake by racial-ethnic group[1]

Brachial measure and fish frequency	White (n = 1059)				Black (n = 619)				Chinese (n = 606)				Hispanic (n = 761)			
	Age-adjusted		Fully adjusted[2]		Age-adjusted		Fully adjusted[2]		Age-adjusted		Fully adjusted[2]		Age-adjusted		Fully adjusted[2]	
	Values	*P*	Values	*P*	Values	*P*	Values	*P*	Values	*P*	Values	*P*	Values	*P*	Values	*P*
Baseline diameter (mm)[3]																
Never or rare	4.35 ± 0.06	0.14	4.40 ± 0.10	0.48	4.51 ± 0.08	0.43	4.52 ± 0.11	0.38	4.33 ± 0.08	0.36	4.53 ± 0.09	0.53	4.48 ± 0.05	0.02	4.50 ± 0.05	0.009
1–3 times/mo	4.16 ± 0.05	—	4.37 ± 0.11	—	4.41 ± 0.06	—	4.57 ± 0.10	—	4.29 ± 0.07	—	4.37 ± 0.08	—	4.45 ± 0.05	—	4.51 ± 0.06	—
1–2 times/wk	4.12 ± 0.05	—	4.39 ± 0.11	—	4.45 ± 0.06	—	4.59 ± 0.11	—	4.26 ± 0.05	—	4.37 ± 0.07	—	4.34 ± 0.07	—	4.41 ± 0.07	—
>2 times/wk	4.20 ± 0.05	—	4.42 ± 0.11	—	4.40 ± 0.07	—	4.59 ± 0.11	—	4.25 ± 0.05	—	4.43 ± 0.07	—	4.27 ± 0.09	—	4.30 ± 0.08	—
Maximum diameter (mm)[4]																
Never or rare	4.37 ± 0.01	0.44	4.37 ± 0.02	0.35	4.59 ± 0.01	0.16	4.60 ± 0.02	0.14	4.46 ± 0.01	0.51	4.44 ± 0.02	0.57	4.61 ± 0.01	0.09	4.61 ± 0.01	0.11
1–3 times/mo	4.38 ± 0.01	—	4.37 ± 0.02	—	4.59 ± 0.01	—	4.59 ± 0.02	—	4.48 ± 0.01	—	4.46 ± 0.01	—	4.60 ± 0.01	—	4.61 ± 0.01	—
1–2 times/wk	4.38 ± 0.01	—	4.37 ± 0.02	—	4.58 ± 0.01	—	4.58 ± 0.02	—	4.46 ± 0.01	—	4.43 ± 0.01	—	4.59 ± 0.01	—	4.59 ± 0.01	—
>2 times/wk	4.38 ± 0.01	—	4.38 ± 0.02	—	4.58 ± 0.01	—	4.59 ± 0.02	—	4.46 ± 0.01	—	4.44 ± 0.01	—	4.60 ± 0.01	—	4.60 ± 0.01	—
FMD change (mm)																
Never or rare	0.18 ± 0.01	0.39	0.17 ± 0.02	0.40	0.16 ± 0.01	0.20	0.18 ± 0.02	0.10	0.19 ± 0.01	0.59	0.15 ± 0.02	0.66	0.19 ± 0.01	0.19	0.19 ± 0.01	0.32
1–3 times/mo	0.19 ± 0.01	—	0.18 ± 0.02	—	0.16 ± 0.01	—	0.17 ± 0.02	—	0.21 ± 0.01	—	0.18 ± 0.01	—	0.18 ± 0.01	—	0.19 ± 0.01	—
1–2 times/wk	0.19 ± 0.01	—	0.18 ± 0.02	—	0.14 ± 0.01	—	0.15 ± 0.02	—	0.19 ± 0.01	—	0.16 ± 0.01	—	0.17 ± 0.01	—	0.18 ± 0.01	—
>2 times/wk	0.19 ± 0.01	—	0.19 ± 0.02	—	0.15 ± 0.01	—	0.16 ± 0.02	—	0.19 ± 0.01	—	0.16 ± 0.01	—	0.18 ± 0.01	—	0.19 ± 0.01	—
FMD change (%)[5]																
Never or rare	4.38 ± 0.22	0.34	4.13 ± 0.49	0.83	3.65 ± 0.23	0.40	4.04 ± 0.42	0.13	4.59 ± 0.31	0.60	3.55 ± 0.42	0.57	4.07 ± 0.19	0.54	4.43 ± 0.20	0.63
1–3 times/mo	4.87 ± 0.15	—	4.40 ± 0.51	—	3.78 ± 0.17	—	3.92 ± 0.41	—	5.13 ± 0.24	—	4.29 ± 0.37	—	3.71 ± 0.20	—	4.36 ± 0.22	—
1–2 times/wk	4.85 ± 0.17	—	4.29 ± 0.52	—	3.36 ± 0.19	—	3.52 ± 0.42	—	4.59 ± 0.18	—	3.75 ± 0.34	—	3.69 ± 0.26	—	4.12 ± 0.26	—
>2 times/wk	4.75 ± 0.17	—	4.29 ± 0.53	—	3.58 ± 0.22	—	3.66 ± 0.44	—	4.70 ± 0.18	—	3.73 ± 0.34	—	4.28 ± 0.35	—	4.48 ± 0.32	—

[1] All values are means ± SDs. FMD, brachial artery flow-mediated dilation.

[2] Multivariate linear regression analysis with adjustment for age, sex, BMI, current smoking status, educational level, and income level.

[3] *P* value for (nonfried fish × race-ethnicity) interaction = 0.24.

[4] Adjusted for baseline artery diameter.

[5] [(Maximum diameter – baseline diameter)/baseline diameter] × 100%.

TABLE 4
Brachial artery measures and plasma phospholipid eicosapentaenoic acid and docosahexaenoic acid (EPA + DHA) concentrations by racial-ethnic group[1]

Brachial measure and EPA + DHA quartile	White (*n* = 380)				Black (*n* = 282)				Chinese (*n* = 558)				Hispanic (*n* = 384)			
	Age-adjusted		Fully adjusted[2]		Age-adjusted		Fully adjusted[2]		Age-adjusted		Fully adjusted[2]		Age-adjusted		Fully adjusted[2]	
	Values	*P*	Values	*P*	Values	*P*	Values	*P*	Values	*P*	Values	*P*	Values	*P*	Values	*P*
Baseline diameter (mm)[3]																
1	4.30 ± 0.07	0.07	4.54 ± 0.16	0.81	4.28 ± 0.14	0.83	4.17 ± 0.18	0.67	4.61 ± 0.11	0.01	4.62 ± 0.11	0.53	4.43 ± 0.06	0.02	4.53 ± 0.06	0.33
2	4.08 ± 0.08	—	4.57 ± 0.17	—	4.40 ± 0.09	—	4.43 ± 0.15	—	4.19 ± 0.07	—	4.36 ± 0.09	—	4.41 ± 0.08	—	4.61 ± 0.08	—
3	4.18 ± 0.11	—	4.53 ± 0.19	—	4.38 ± 0.08	—	4.32 ± 0.15	—	4.28 ± 0.05	—	4.46 ± 0.08	—	4.17 ± 0.10	—	4.42 ± 0.09	—
4	4.05 ± 0.11	—	4.52 ± 0.19	—	4.37 ± 0.10	—	4.36 ± 0.17	—	4.18 ± 0.05	—	4.44 ± 0.08	—	4.20 ± 0.12	—	4.47 ± 0.10	—
Maximum diameter (mm)[4]																
1	4.37 ± 0.01	0.91	4.34 ± 0.03	0.85	4.50 ± 0.02	0.10	4.49 ± 0.03	0.03	4.44 ± 0.02	0.40	4.41 ± 0.02	0.61	4.55 ± 0.01	0.47	4.54 ± 0.01	0.60
2	4.38 ± 0.01	—	4.34 ± 0.03	—	4.52 ± 0.01	—	4.51 ± 0.02	—	4.45 ± 0.01	—	4.42 ± 0.02	—	4.54 ± 0.01	—	4.54 ± 0.01	—
3	4.36 ± 0.01	—	4.32 ± 0.03	—	4.52 ± 0.01	—	4.51 ± 0.02	—	4.45 ± 0.01	—	4.43 ± 0.01	—	4.55 ± 0.01	—	4.54 ± 0.01	—
4	4.38 ± 0.01	—	4.34 ± 0.03	—	4.54 ± 0.01	—	4.53 ± 0.02	—	4.43 ± 0.01	—	4.41 ± 0.01	—	4.53 ± 0.01	—	4.53 ± 0.02	—
FMD change (mm)																
1	0.19 ± 0.01	0.99	0.16 ± 0.03	0.87	0.13 ± 0.02	0.11	0.13 ± 0.03	0.04	0.18 ± 0.02	0.63	0.14 ± 0.02	0.69	0.19 ± 0.01	0.73	0.18 ± 0.01	0.75
2	0.20 ± 0.01	—	0.17 ± 0.03	—	0.15 ± 0.01	—	0.15 ± 0.02	—	0.20 ± 0.01	—	0.17 ± 0.02	—	0.18 ± 0.01	—	0.17 ± 0.01	—
3	0.18 ± 0.01	—	0.15 ± 0.03	—	0.15 ± 0.01	—	0.16 ± 0.02	—	0.20 ± 0.01	—	0.17 ± 0.01	—	0.19 ± 0.01	—	0.19 ± 0.02	—
4	0.20 ± 0.01	—	0.16 ± 0.03	—	0.17 ± 0.01	—	0.18 ± 0.02	—	0.19 ± 0.01	—	0.15 ± 0.01	—	0.18 ± 0.01	—	0.17 ± 0.02	—
FMD change (%)[5]																
1	4.78 ± 0.24	0.64	3.61 ± 0.76	0.86	3.17 ± 0.40	0.15	3.37 ± 0.65	0.06	4.07 ± 0.40	0.90	3.16 ± 0.53	0.65	4.41 ± 0.19	0.59	4.11 ± 0.26	0.98
2	5.22 ± 0.27	—	3.71 ± 0.78	—	3.58 ± 0.25	—	3.59 ± 0.55	—	4.96 ± 0.27	—	4.03 ± 0.37	—	4.31 ± 0.25	—	3.86 ± 0.33	—
3	4.64 ± 0.36	—	3.29 ± 0.85	—	3.72 ± 0.23	—	3.97 ± 0.53	—	4.96 ± 0.19	—	3.92 ± 0.38	—	4.89 ± 0.34	—	4.47 ± 0.39	—
4	5.17 ± 0.39	—	3.69 ± 0.88	—	3.88 ± 0.28	—	4.14 ± 0.59	—	4620 ± 0.17	—	3.55 ± 0.36	—	4.40 ± 0.38	—	3.93 ± 0.43	—

[1] All values are means ± SDs. FMD, brachial artery flow-mediated dilation. Concentrations of plasma phospholipid EPA and DHA (expressed as percentages of total fatty acids) were summed and ranked into quartiles from lowest to highest on the basis of the sample range.

[2] Multivariate linear regression analysis with adjustment for age, sex, BMI, current smoking status, educational level, and income level.

[3] *P* value for (EPA + DHA × race-ethnicity) interaction = 0.92.

[4] Adjusted for baseline artery diameter.

[5] [(Maximum diameter − baseline diameter)/baseline diameter] × 100%.

To our knowledge, the current study is unique in that it examined fish consumption separately in men and women of 4 different racial-ethnic groups and also examined plasma phospholipid EPA + DHA concentrations. Although our results are not consistent with other research that showed a significant improvement in FMD after feeding fish oil supplements to subjects (21, 22), our study differed in that dietary whole fish was examined. Furthermore, this was not a feeding trial that examined a clinical outcome, but rather, this study was conducted in an ethnically diverse cohort who consumed their own native diet. Although the observed differences between men and women were unexpected, the inconsistency between men and women of similar racial-ethnic groups suggests that this disparity is unlikely to be fully explained by food-preparation methods alone (ie, Chinese men and women, whom we expected would have similar methods of fish preparation, differed in FMD results; this was also the case for Hispanic men compared with women). The similar results noted between brachial artery measures and plasma phospholipid EPA + DHA concentrations, which were correlated with nonfried fish intake, further support these findings.

The strengths of this study include the ethnically diverse population, the inclusion of men and women, the large overall sample size, and the availability of detailed dietary information as well as objective measures of endothelial function. The limitations of the study include the observational cross-sectional study design with its known inability to infer causation and the potential for temporal bias, as well as several limitations in the MESA diet questionnaire. Because the diet questionnaire was not designed to specifically assess fish and long-chain fatty acid intake, some potentially key details were lacking, such as separate data on amounts of oily fish consumed, the freshness of the fish, and the fish preparation and cooking methods. Furthermore, like any observational study, there remains the possibility of residual confounding for factors (such as health status) or differential recall related to food intakes that could have meaningful effects on the observed results. It is also possible that our findings are reflective of spurious associations that resulted from multiple testing. However, despite these potential shortcomings, previous data from MESA speak to the construct validity of the assessment of fish intake in this population (27, 36). Finally, we must also consider the possibility of measurement error within the multiple measures of brachial artery diameters, which could have diminished our ability to observe significant associations. Although the intraindividual variability of FMD is notable (50), the cross-sectional design of this large population study reduced the potential significance of such an inconsistency.

In conclusion, this study adds to the small but growing body of evidence that diet may have differential effects on cardiovascular outcomes in women compared with in men. Within this cohort of mixed racial-ethnic groups without known coronary artery disease, the associations of nonfried fish consumption with brachial artery measures varied by sex. Similar associations were observed between plasma phospholipid EPA + DHA concentrations and brachial artery measures. Additional analyses provided suggestive evidence of differences by race-ethnicity as well as race-ethnicity by sex. Future studies are warranted to clarify the extent to which sex may modify the relation between polyunsaturated fatty acids and cardiovascular outcomes.

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REFERENCES

1. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989;2:757–61.
2. Daviglus ML, Stamler J, Orencia AJ, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. N Engl J Med 1997;336:1046–53.
3. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002;106:2747–57.
4. Smith SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006;113:2363–72.
5. Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. Am J Med 2002;112:298–304.
6. Marchioli R, Marfisi RM, Borrelli G, et al. Efficacy of n−3 polyunsaturated fatty acids according to clinical characteristics of patients with recent myocardial infarction: insights from the GISSI-Prevenzione trial. J Cardiovasc Med (Hagerstown) 2007;8(suppl 1):S34–7.
7. Calder PC. n−3 Fatty acids and cardiovascular disease: evidence explained and mechanisms explored. Clin Sci 2004;107:1–11.
8. Ferrucci L, Cherubini A, Bandinelli S, et al. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. J Clin Endocrinol Metab 2006;91:439–46.
9. Lankinen M, Schwab U, Erkkilä A, et al. Fatty fish intake decreases lipids related to inflammation and insulin signaling–a lipidomics approach. PLoS ONE 2009;4:e5258.
10. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB. Habitual dietary intake of n−3 and n−6 fatty acids in relation to inflammatory markers among US men and women. Circulation 2003;108:155–60.
11. Khan F, Elherik K, Bolton-Smith C, et al. The effects of dietary fatty acid supplementation on endothelial function and vascular tone in healthy subjects. Cardiovasc Res 2003;59:955–62.
12. Goode GK, Garcia S, Heagerty AM. Dietary supplementation with marine fish oil improves in vitro small artery endothelial function in hypercholesterolemic patients: a double-blind placebo-controlled study. Circulation 1997;96:2802–7.
13. Harris WS, Rambjør GS, Windsor SL, Diederich D. n−3 fatty acids and urinary excretion of nitric oxide metabolites in humans. Am J Clin Nutr 1997;65:459–64.
14. Bugiardini R, Manfrini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease: a study of women with chest pain and normal coronary angiograms. Circulation 2004;109:2518–23.
15. Vogel RA, Corretti MC, Plotnick GD. A comparison of brachial artery flow-mediated vasodilation using upper and lower arm arterial occlusion in subjects with and without coronary risk factors. Clin Cardiol 2000;23:571–5.

16. Neunteufl T, Heher S, Katzenschlager R, et al. Late prognostic value of flow-mediated dilation in the brachial artery of patients with chest pain. Am J Cardiol 2000;86:207–10.
17. Yeboah J, Crouse JR, Hsu F, Burke GL, Herrington DM. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. Circulation 2007;115:2390–7.
18. Yeboah J, Folsom AR, Burke GL, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. Circulation 2009;120:502–9.
19. Anderson TJ. Prognostic significance of brachial flow-mediated vasodilation. Circulation 2007;115:2373–5.
20. Shechter M, Issachar A, Marai I, et al. Long-term association of brachial artery flow-mediated vasodilation and cardiovascular events in middle-aged subjects with no apparent heart disease. Int J Cardiol 2009;134:52–8.
21. Goodfellow J, Bellamy MF, Ramsey MW, Jones CJ, Lewis MJ. Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. J Am Coll Cardiol 2000;35:265–70.
22. Shah AP, Ichiuji AM, Han JK, et al. Cardiovascular and endothelial effects of fish oil supplementation in healthy volunteers. J Cardiovasc Pharmacol Ther 2007;12:213–9.
23. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.
24. Nettleton JA, Steffen LM, Mayer-Davis EJ, et al. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr 2006;83:1369–79.
25. Mayer-Davis EJ, Vitolins MZ, Carmichael SL, et al. Validity and reproducibility of a food frequency interview in a Multi-Cultural Epidemiology Study. Ann Epidemiol 1999;9:314–24.
26. Nettleton JA, Rock CL, Wang Y, Jenny NS, Jacobs DR. Associations between dietary macronutrient intake and plasma lipids demonstrate criterion performance of the Multi-Ethnic Study of Atherosclerosis (MESA) food-frequency questionnaire. Br J Nutr 2009;102:1220–7.
27. Chung H, Nettleton JA, Lemaitre RN, et al. Frequency and type of seafood consumed influence plasma (n−3) fatty acid concentrations. J Nutr 2008;138:2422–7.>
28. Siscovick DS, Lemaitre RN, Mozaffarian D. The fish story: a diet-heart hypothesis with clinical implications: n−3 polyunsaturated fatty acids, myocardial vulnerability, and sudden death. Circulation 2003;107:2632–4.
29. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. Clin Chem 1995;41:264–70.
30. Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n−3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am J Clin Nutr 2003;77:319–25.
31. Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus, Diabetes Care 2003;26:3160–7.
32. Pawlosky R, Hibbeln J, Lin Y, Salem N. n−3 fatty acid metabolism in women. Br J Nutr 2003;90:993–4, discussion 994–5.
33. Childs CE, Romeu-Nadal M, Burdge GC, Calder PC. Gender differences in the n−3 fatty acid content of tissues. Proc Nutr Soc 2008;67:19–27.
34. Woo KS, McCrohon JA, Chook P, et al. Chinese adults are less susceptible than whites to age-related endothelial dysfunction. J Am Coll Cardiol 1997;30:113–8.
35. Yeboah J, Crouse JR, Bluemke DA, et al. Endothelial dysfunction is associated with left ventricular mass (assessed using MRI) in an adult population (MESA). J Hum Hypertens (Epub ahead of print 18 March 2010).
36. He K, Liu K, Daviglus ML, et al. Associations of dietary long-chain n−3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol 2009;103:1238–43.
37. Siscovick DS, Raghunathan TE, King I, et al. dietary intake and cell membrane levels of long-chain n−3 polyunsaturated fatty acids and the risk of primary cardiac arrest. JAMA 1995;274:1363–7.
38. Li Z, Otvos JD, Lamon-Fava S, et al. Men and women differ in lipoprotein response to dietary saturated fat and cholesterol restriction. J Nutr 2003;133:3428–33.
39. Walden CE, Retzlaff BM, Buck BL, Wallick S, McCann BS, Knopp RH. Differential effect of National Cholesterol Education Program (NCEP) Step II diet on HDL cholesterol, its subfractions, and apoprotein A-I Levels in hypercholesterolemic women and men after 1 year: The beFIT Study. Arterioscler Thromb Vasc Biol 2000;20:1580–7.
40. Mozaffarian D, Rimm EB, Herrington DM. Dietary fats, carbohydrate, and progression of coronary atherosclerosis in postmenopausal women. Am J Clin Nutr 2004;80:1175–84.
41. Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA 2002;287:1815–21.
42. Meng L, Wilkens L, Kolonel L. Abstract 1404: Fish consumption and ethnic differences in coronary heart disease mortality in a multiethnic cohort. Circulation 2009;120(18_MeetingAbstracts):S498-a. Available from: http://circ.ahajournals.org/cgi/content/meeting_abstract/120/18_MeetingAbstracts/S498-a (cited 30 August 2010).
43. Crowe FL, Skeaff CM, Green TJ, Gray AR. Serum n−3 long-chain PUFA differ by sex and age in a population-based survey of New Zealand adolescents and adults. Br J Nutr 2008;99:168–74.
44. Dewailly É, Blanchet C, Gingras S, et al. Relations between n−3 fatty acid status and cardiovascular disease risk factors among Quebecers. Am J Clin Nutr 2001;74:603–11.
45. Dewailly E, Blanchet C, Lemieux S, et al. n−3 Fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik. Am J Clin Nutr 2001;74:464–73.
46. Pawlosky RJ, Hibbeln JR, Lin Y, et al. Effects of beef- and fish-based diets on the kinetics of n−3 fatty acid metabolism in human subjects. Am J Clin Nutr 2003;77:565–72.
47. Burdge GC, Wootton SA. Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. Br J Nutr 2002;88:411–20.
48. Brossard N, Croset M, Pachiaudi C, Riou JP, Tayot JL, Lagarde M. Retroconversion and metabolism of [13C]22:6n−3 in humans and rats after intake of a single dose of [13C]22:6n−3-triacylglycerols. Am J Clin Nutr 1996;64:577–86.
49. Das UN. Essential fatty acids: biochemistry, physiology and pathology. Biotechnol J 2006;1:420–39.
50. De Roos NM, Bots ML, Schouten EG, Katan MB. Within-subject variability of flow-mediated vasodilation of the brachial artery in healthy men and women: implications for experimental studies. Ultrasound Med Biol 2003;29:401–6.